Mike is a social professor of medicine and internal medicine and medical oncology. He shares patients or cancer patients, as part of the smiling prostate, your logic cancer program. Alright, joining Allen 2009 Doctor Hertz was instructor of medicine at Harvard and attending physician in medicine at the Massachusetts General Hospital. MIKES graduate of Harvard College. He received his doctorate degree in cell Biology from Rockville University’s and medical degree from Cornell University.
He completed a fellowship in Archology,

Dana Farber and postdoctoral fellowship in Biology, the Masters in Massachusetts,

Channel MIT Institution might still be talking about the silk yellow cell therapy program for solid tumors.

Mike take it away.

Thanks, Dan.

Yeah, thanks everyone for inviting us from that from the therapy dog to talk.

I’m going to talk obviously about the solid tumor side and then the other half is going to be here as this would be talking about liquid.
So were the newest art. And we really started right before covid so we don’t have a whole lot of trials open, so I think that this talk is going to be sort of short on data, but I hope it’s going to be long on potential. OK, let me see if I can move my thing forward here in my disclosures. So the main therapies I’m going to talk about today are car T cells and tumor infiltrating lymphocytes. And I think that everybody is somewhat familiar with these terms.
00:01:32.206 --> 00:01:34.340 a lot about these so far,

NOTE Confidence: 0.7214773

00:01:34.340 --> 00:01:35.930 but but they’re really quite

NOTE Confidence: 0.7214773

00:01:35.930 --> 00:01:36.566 different therapies,

NOTE Confidence: 0.7214773

00:01:36.570 --> 00:01:38.818 and I do want to talk a little

NOTE Confidence: 0.7214773

00:01:38.818 --> 00:01:40.720 bit about the basic biology.

NOTE Confidence: 0.7214773

00:01:40.720 --> 00:01:42.628 So for those who are immunologists,

NOTE Confidence: 0.7214773

00:01:42.630 --> 00:01:43.587 bear with us.

NOTE Confidence: 0.7214773

00:01:43.587 --> 00:01:45.182 Maybe read the newspaper for

NOTE Confidence: 0.7214773

00:01:45.182 --> 00:01:47.443 a minute or two while I give

NOTE Confidence: 0.7214773

00:01:47.443 --> 00:01:49.003 you my very simple oncologist.

NOTE Confidence: 0.7214773

00:01:49.010 --> 00:01:50.171 View of immunology.

NOTE Confidence: 0.7214773

00:01:50.171 --> 00:01:52.880 So adaptive immunity is where T cells

NOTE Confidence: 0.7214773

00:01:52.950 --> 00:01:55.055 primarily recognize things that are

NOTE Confidence: 0.7214773

00:01:55.055 --> 00:01:57.570 foreign and used in attack them.

NOTE Confidence: 0.7214773

00:01:57.570 --> 00:01:57.909 Now,
one of the reasons we don’t attack ourselves is that we’re always taking little chunks of our proteins, expressing them on the surface in something called the major histocompatibility complex, the T cell receptors. Basically, when we know our own a little bit? After that all the T cell receptors that we have the T cells. That that recognized groups. That recognize. The energy is well, get deleted,
or at least they get turned off OK, so generally we don’t respond to our own antigens, but if you get a foreign antigen like a bacteria, what happens is let’s say if they go into a cell, the cell chops up the proteins. The proteins get put on MHC and the T cell receptor is going to recognize there’s going to be a strong interaction, but that isn’t enough to actually cause killing. It’s only when you get something
called costimulation OK, and that’s via another pathway. Another set of receptors. And then you actually get killed all right. So how can we use that information to kill cancer cells? So let me say a little bit more and go a little bit more in depth into the T cell receptor signaling first. So this is a schematic of the T cell receptor, the Alpha beta chains are the ones that actually recognize the antigens and MHC, and there are signaling molecules, the Zeta chain and the associated CD3. So T cell receptors only recognize proteins.
They only work if the antigen is expressed is presented by MHC. And they require Co stimulation. And as I said, the signaling are through these two things. Antibodies another way that we recognize things that were formed were quite differently. They can recognize any type of management doesn’t have protein. They don’t use MHC, and antibodies are much, much stronger, their interactions with their antigens and T cell receptors are with their antigen that makes the interactions up.
to 1000 and 10,000 fold stronger in fact.

So someone had the bright idea of taking the back end of a T cell receptor and connecting it to the front end of an antibody. And we call those guys chimeric antigen receptors and so this is the first generation car and this is actually in the 1990s. It was awhile ago so this is the antibody. OK on the outside of the cell and this is part of the solar spectrum. The inside of the cell worked a little bit, but not terribly well. A huge breakthrough though came in the second generation.
And here what was done is they add a domain to the protein of CD 28. And what’s that? Whoops, that of course is the costimulatory signal, and so when you put the customer let costimulator right in it, these are much, much more powerful, these are really what we mostly use today. There are even stronger ones. The third generations that use two costimulatory signals, and there’s the 4th generation, which is a combination of cars plus other genes that are put in.
00:04:48.765 --> 00:04:50.787 to make the cells work better.
NOTE Confidence: 0.8157049
00:04:50.790 --> 00:04:53.300 So.
NOTE Confidence: 0.8157049
00:04:53.300 --> 00:04:55.256 When you actually the mechanics of
NOTE Confidence: 0.8157049
00:04:55.256 --> 00:04:57.569 this and in patients are complicated,
NOTE Confidence: 0.8157049
00:04:57.570 --> 00:04:59.706 just like all cell therapies are,
NOTE Confidence: 0.8157049
00:04:59.710 --> 00:05:01.130 whether it’s transplant or
NOTE Confidence: 0.8157049
00:05:01.130 --> 00:05:02.195 something like this.
NOTE Confidence: 0.8157049
00:05:02.200 --> 00:05:05.760 In this case you need to isolate the T cells.
NOTE Confidence: 0.8157049
00:05:05.760 --> 00:05:08.070 They have to get activated and then
NOTE Confidence: 0.8157049
00:05:08.070 --> 00:05:09.893 their transduced with the chimeric
NOTE Confidence: 0.8157049
00:05:09.893 --> 00:05:11.808 antigen receptor and then expanded
NOTE Confidence: 0.8157049
00:05:11.808 --> 00:05:14.041 and then reinfused in the meantime
NOTE Confidence: 0.8157049
00:05:14.041 --> 00:05:15.751 patients get lympho depleted and
NOTE Confidence: 0.8157049
00:05:15.751 --> 00:05:19.268 the reason for that is that.
NOTE Confidence: 0.8157049
00:05:19.270 --> 00:05:20.155 Probably twofold reasons.
NOTE Confidence: 0.8157049
00:05:20.155 --> 00:05:21.040 For some reasons,
00:05:21.040 --> 00:05:22.410 you’re actually treating the cancer
00:05:22.410 --> 00:05:24.290 to some degree by lymphodepleting,
00:05:24.290 --> 00:05:26.650 but that isn’t the case for all cancers.
00:05:26.650 --> 00:05:27.240 For some,
00:05:27.240 --> 00:05:29.954 you’re doing it to have a niche for the
00:05:29.954 --> 00:05:32.546 T cells to actually live in and grow it.
00:05:32.550 --> 00:05:33.730 As you might imagine,
00:05:33.730 --> 00:05:35.500 this does not take a day.
00:05:35.500 --> 00:05:36.716 This takes several weeks,
00:05:36.716 --> 00:05:39.192 so one of the things about this kind
00:05:39.192 --> 00:05:41.243 of treatment is patients have to be
00:05:41.243 --> 00:05:43.245 well enough to survive those weeks and
00:05:43.245 --> 00:05:45.229 to be able to tolerate the therapy.
00:05:47.400 --> 00:05:49.974 I’m not going to go into this in detail,
00:05:49.980 --> 00:05:51.793 but there are a lot of toxicities
associated with these treatments.

The three famous ones are cited kind of release syndrome,

which has to do with a lot of T cells at the same time,

seeing antigen and then causing lots of cytokines to go into the circulation.

There’s also neurotoxicity called crests or cans and probably the most severe of these HLH.

Alright, So what are we doing at Yale?

We have one party study open right now for solid tumors.

This is a kidney cancer trial done by the company, CRISPR Therapeutics.

It’s anti CD 70 which is highly
expressed on clear cell kidney cancers and then there’s some expression on a few lymphoid type of cells. Now it’s very long name for the trial. The reason is that it’s actually a little more complicated than even what I described before. ’cause these are allogeneic engineered T cells. And what does that mean? So these are T cells that actually don’t come from the patient they come from. Sort of healthy weight healthy donors in whom there they’re having the car put into their own T cells and they this company using CRISPR CAS nine.
I think a lot of us are familiar with that to knock out certain other genes in these T cells to make them work in us. So what do I mean by that? Well, if you take someone else T cells and put them into you, they will attack you and you will attack it. It won’t be an effective therapy. They will get destroyed pretty quickly by the endogenous immune system, and they’re going to have off target effects via their T cell receptors, potentially. So what they’ve done this CRISPR therapeutics is in addition to
They've also put in CRISPR.
They've removed the T cell receptor OK.
They've also removed something called beta two microglobulin,
which is part of MHC class one, and the result is that our immune system doesn't recognize that it very well except by some something.
All natural killer cells.
It doesn't do that much,
and it doesn't really recognize us except via the anti CD 7.
Alright,
so there are a bunch of advantages here
of using T cells from someone else
NOTE Confidence: 0.77227306
and not from the patient one is speed.
NOTE Confidence: 0.77227306
These cells are waiting.
NOTE Confidence: 0.77227306
The patients don’t have to wait.
NOTE Confidence: 0.77227306
Secondly,
NOTE Confidence: 0.77227306
these cells are for someone with
NOTE Confidence: 0.77227306
an immune with Acton intact immune
NOTE Confidence: 0.77227306
system and a lot of patients with
NOTE Confidence: 0.77227306
extensive cancers may not have
NOTE Confidence: 0.77227306
intact immune systems and the T
NOTE Confidence: 0.77227306
cells may be somewhat dysfunctional,
NOTE Confidence: 0.77227306
and obviously it leads to the
NOTE Confidence: 0.77227306
potential for more of a drug,
NOTE Confidence: 0.77227306
something that can be done with
NOTE Confidence: 0.77227306
high levels of production out there
NOTE Confidence: 0.77227306
for everybody we’ve enrolled.
One patient, we’re going to be enrolling one patient another patient in a few months, or at the dose escalation phase, and we’ll see how this trial goes. What else is going on at yelled, oh, oh, sorry before I, I go there, let me just. Say that So what? Some of the challenges are for car T cells. Specifically in solid tumors. Well, in general there can be an issue with persistence. The car T cells. They may not last, but these are big issues for solitaire.
So one there is almost no answers

And when you give something like CAR T

it’s very likely that the tumor

will just mutate or or lower

expression of that antigen.

In addition to that,

the micro environment of the tumor is

very toxic to a lot of immune cells,

including T cells.

It’s hard to infiltrate into a lot of tumors.

There’s a lot of necrosis.

Many of the cells have low blood supply,

e etc.
And finally, the toxicity is that I sort of mentioned before. So one of the things that's being done here is being done by the lab of City Chen. His is the only 11 going to talk about, but it's worth pointing out there are many labs here working on car T type therapies. City Shuns Lab has developed a modular, high throughput way of developing cartis, and it's the system that again is very complex. There's a there's no time for me to describe it and be I
wouldn't be able to do very well anyway.

But this is a slide from CD,

this is his own system that he is designed using adeno associated virus.

To make parties, it enables rapid building of new modules because because modular we can put in many different cars into a lot of cells and look at them in parallel. And it also allows for knockout of other genes in the cell just to make to try to improve the cell’s capabilities.

And therefore we’re looking for is superior cancer killing based
on a lot of the platforms that are used now in the short term goal, of course, is to generate better parties against kidney cancer. He’s actually looking at kidney cancer, which is great. ’cause that’s a lot of what I’m interested in, and we’re also working with Doctor Krueger on this area. Cougar, but also he can engineer in safety control so that if the T cells are causing some of these severe toxicities, they can be turned off. And you know the long term goal, of course, is to optimize better
00:10:55.642 --> 00:10:57.050 parties across solid tumors.
NOTE Confidence: 0.8152212
00:10:57.050 --> 00:11:00.070 Anan maybe liquid tumors too.
NOTE Confidence: 0.8152212
00:11:00.070 --> 00:11:01.906 In the first step of that,
NOTE Confidence: 0.8152212
00:11:01.910 --> 00:11:04.059 hopefully will be once his lab develops,
NOTE Confidence: 0.8152212
00:11:04.060 --> 00:11:05.896 but he makes a great car.
NOTE Confidence: 0.8152212
00:11:05.900 --> 00:11:07.742 Is for us to actually put
NOTE Confidence: 0.8152212
00:11:07.742 --> 00:11:08.970 it into trials alright,
NOTE Confidence: 0.8152212
00:11:08.970 --> 00:11:10.951 moving on to till let’s go back
NOTE Confidence: 0.8152212
00:11:10.951 --> 00:11:12.659 very quickly again into immunity.
NOTE Confidence: 0.8152212
00:11:12.660 --> 00:11:14.766 So remember something for and it’s
NOTE Confidence: 0.8152212
00:11:14.766 --> 00:11:17.092 a strong interaction by the T cell
NOTE Confidence: 0.8152212
00:11:17.092 --> 00:11:19.087 receptor and the MHC complex you get
NOTE Confidence: 0.8152212
00:11:19.148 --> 00:11:21.266 Co stimulation and you get killing.
NOTE Confidence: 0.8152212
00:11:21.270 --> 00:11:21.523 Alright,
NOTE Confidence: 0.8152212
00:11:21.523 --> 00:11:24.243 but how do you get a T cell that actually
NOTE Confidence: 0.8152212
00:11:24.243 --> 00:11:26.517 kills something that’s not for it,
As mentioned before, we don’t interact very well with our own antigens. Now, cancer has sort of solved that a little bit for us in that cancer proteins are often mutated because cancer causing mutations and therefore the peptides actually can look for and so you can actually get T cells to kill. As we all know though, it doesn’t really work very well on its own. We need to give things like immune
checkpoint inhibitors because of the toxic micro environment, so I thought that was developed back in the 1980s. Was well, maybe if we take the two T cells out of that environment, grow them up, enhance their function with cytokines, maybe we can cause cell killing if we re-infuse those T cells. And that’s what ‘til therapy is. So much like I described, the car T cells, you respect the tumors from patients. T cells are isolated from those tumors. They are activated and expanded in vitro,
NOTE Confidence: 0.8152212
00:12:20.520 --> 00:12:21.948 generally using Interleukin 2,
NOTE Confidence: 0.8152212
00:12:21.948 --> 00:12:24.090 but there are other interventions we
NOTE Confidence: 0.8152212
00:12:24.151 --> 00:12:26.495 use and then they reinfuse with the patient.
NOTE Confidence: 0.8152212
00:12:26.500 --> 00:12:27.493 In the meantime,
NOTE Confidence: 0.8152212
00:12:27.493 --> 00:12:29.148 agents have been limited depleted,
NOTE Confidence: 0.8152212
00:12:29.150 --> 00:12:31.496 which is extremely important for this
NOTE Confidence: 0.8152212
00:12:31.496 --> 00:12:33.953 therapy because we not only have to
NOTE Confidence: 0.8152212
00:12:33.953 --> 00:12:36.460 have a niche for the cells to go into,
NOTE Confidence: 0.8152212
00:12:36.460 --> 00:12:39.826 we have to get rid of T regulatory cells.
NOTE Confidence: 0.8152212
00:12:39.830 --> 00:12:41.050 And the Immune system Act
NOTE Confidence: 0.8152212
00:12:41.050 --> 00:12:42.270 as a sighted kind sink,
NOTE Confidence: 0.8152212
00:12:42.270 --> 00:12:44.111 sucking up all the good side accounts
NOTE Confidence: 0.8152212
00:12:44.111 --> 00:12:46.170 that we want to go to these T cells.
NOTE Confidence: 0.8152212
00:12:46.170 --> 00:12:48.662 'cause when we infuse these T cells
NOTE Confidence: 0.8152212
00:12:48.662 --> 00:12:50.828 we give patients in alluding to.
NOTE Confidence: 0.8152212
Now before I move on with that with till I think a lot of the time when I tell people that were interested in cell therapies, they say oh it’s cortisol therapy. But there’s a huge difference between CAR T cell therapies and tilsen. As some examples. You know, car T cells are MHC totally independent right there using an antibody, whereas ’til therapy is totally dependent. CAR T cells don’t? They can look at sugars or other non protein antigens. Tills do not.
Cars are pretty ineffective at looking at intracellular proteins. They’re working on that, so maybe we’ll get there one day, but right now they can’t really recognize a lot of the proteins. And the key thing is that you know, till can look at any antigens that they see. So for example, when we take tumors out of patience and isolate the lymphocytes from those, that’s going to be a diverse, diverse type of T cells, probably recognizing multiple different antigens.
And, as I said before, a big disadvantage of car T cells. Is that you can lose the one antigen they recognized in their useless and that may not be as big of an issue with 'til therapies. And Lastly, there toxicities are quite different. Alright, So what are we doing at Yale? We have a trial right now for looking at triple negative breast cancer. This is an IIT that I'm doing with IMS Therapeutics. This is the first dedicated breast cancer till trial world we’ve been. We’ve enrolled two patients so far,
and one of the reasons were interesting.

Breast is that there’s lab here. Tristan Park, who’s a surgical oncologist here, an expert on breast cancer and on breast cancer cell therapies? Who’s actually? Looking at the samples we get analyzing for the immune infiltrates and working with us on the trial. Just to say a little bit more about what it actually entails. It’s there’s a lot of for any sort of cell therapy.

There’s a lot of work that goes into
it because these are complicated therapies that require a good timing so you know once a patient signs consent, they have to get their surgeries. Only then do you initiate. Of course the till culture, it’s going to be going for several weeks, and once you know the till is growing appropriately, only then are you going to limited Lee the patient and then infuse that into the patient. And then of course, as I said, these people require oil to afterwards,
and they’re going to be in the hospital for a lot of this because they’re going to depleted and then once they recover, we follow them. So, how might we improve some of these things? I think infusion and reception isolation. That’s not where the money is, but clearly we can maybe improve activating and expanding these cells and make them better killers. And the people who are the best at growing up and activating these cells.
Of course that you are the people of the

Advanced Therapy Lab run by Alexi Burst.

Never die across and they have a huge amount of expertise over many years.

Looking at till type therapies.

They’ve grown up a lot of different cell products for use in patients,

and I actually hold Inds for growing Melanoma till,

but of course they actually did it and we’re working together right now and we’re working together right now

to grow up lung cancer till four,

ideally to eventually put into patients.

Just quickly to point out,

they are very good at growing up selves.
This is 1 experiment which they actually separated out the PD one actually separated out the PD one positive from negative cells and show a lot of expansion in both of them and this just kind of shows one experiment of theirs that the cells they get are actually quite good. So here till they’ve isolated out and these are assays for interferon gamma production which is an essay of sort of it’s a surrogate for cell killing and when you take this pill and you put him. Alone, they don’t make a lot of interferon gamma.
As soon as you put them with autologous tumor, or they recognize antigens in the setting of MHC, they make tons of interferon gamma and then if you give them someone else's tumor that has emerged, they don't recognize they don't kill. So they're very good at making cells that kill and kill specifically, which is exactly what we need.

So what can we do to actually improve things? To make these, what are we interested in doing here? Yale to improve these therapies?
doing experiments to look at adjusting
the growth medium that that they do
it in different cytokine combinations,
different levels of cytokines and
those experiments are ongoing.
But. It’s actually striking how
little we know about what happens
between when we take the cells out
of a person and we expand them.
We don’t really know
which cells get expanded.
We don’t know whether the T cell maturation
states whether they are more naive or more.
Effectors dictate which
cells that expanded.
We don’t know how this concept of T cell exhaustion relates to expansion, and we have very little idea about how homogeneous or heterogeneous that essential traits are between tumors or between tumor types. So can we actually do experiments to figure some of this stuff out? And the approach that we’re going to take here, and we’ve actually begun taking, is to do single cell RNA sequencing and paired with TCR sequencing so that we can follow specific T cell clones through growth and figure
out which maturation phenotypes are the ones that grow the best. And whether exhaustion has an effect, one it’s being done beginning, and then we’re going to do this across a number of subjects, so I should say that that’s already been done a little bit. One of his graduate students, and I’ll be doing some of these studies on long till. But really, the person doing this, Ben Lewin, the Hafler lab.

I have no time around this,
so I don’t know where I am on time and

someone told me I’ve got a little time.

OK,

good.

So let me say one last set of

experiments that are being done at Yale.

Looking at some basic science that could

have a big impact on T cell therapies.

And by the way, I should point out that,

you know, I’ve mentioned a

few people who are doing work,

but there are many others doing work at Yale.

I they don’t have time unfortunately,

but but I don’t mean to

leave other people out.

We’re doing really vital stuff that
in fact probably there are a lot of things I don’t know about that.
I wish I did.
So one of the things that Sam Katz’s lab is working on is the idea of mRNA reprogramming?
The advantages of this technique is that you can do multiple RNAs at once.

so he’s using something called crisper I which is a crisper based technique to knock down genes but not to actually cause mutations or changes the actual DNA.
Sorry bout that. The other thing about this of course is when you do these things by RNA. RNA is temporary, so there are pluses to that and minuses to that. The pluses are that it’s a lot safer. Not permanently altering itself. OK, the negative, however, is that it’s only temporary, so if you want to have effects that last a long time, this might not be the method to do it. But you can imagine situations where using this kind of technique you could really turbocharge a cell for short period of time.
So for example, we could have a car T cell. And you could use his technique to make the groups make them particularly proliferative at the time at inside accounts, for example to happen particularly powerful and killing stimulators of other things, you could have inhibitors of negative regulators, and in fact Sam is shown in his lab and from Weismans lab that for example they can at the same time using their CRISPR RNA I techniques.
to increase IL two in a cell.

And decrease BCL type proteins which are made up tactic proteins.

So again when you think about what I’ve talked about so far with, let’s say the city Chen Lab in which they can do multiple different things to design sort of permanent T cells, that are particularly powerful.

You could also imagine adding in these M RNA’s to those same cells and making turbochargers even more so.

There’s a huge amount of combinatorial things that we could do.
and there’s a lot of excitement for all those things.

Last but certainly not least, I just want to acknowledge all that people have been doing a lot of work.

So what first assault therapy DART 3 docs? Who do it right now or are nearest Stewart and I Alex is our CDT N as fantastic Sharon days.

Who do it right now or are nearest research nurse Ann Pavan or CRA.

I’m not impressed but and then we have an amazing team here doing, you know regulatory and pharmacy etc.

Also, of course, the AC T lab.
Which you know is really going to be the people developing.

Sorry the next therapies that we do here, I mentioned the Melanoma team because, really, we’ve been doing till at Yale for very long time. And the person who got us started here was Mary Otional and a lot of the ideas that I talked about with regards to how to study these things really came from Mario. Harriet has done the most to have anybody here and has done a huge amount and Sarah Weiss has seen. A lot of the patients as well,
Katrina Bezak, is the person who is really a point person for a lot of salt therapies here, and she’s actually also key for setting us up for. As I said, the very very likely approval of heart till in Melanoma people probably don’t know this, but we have our own something called CDC which is for cell therapies. It’s a committee to look at really usage and whether we have the capability and the capacity. To do all the different trials we want to do,
none of this would be possible without the nursing staff on 11/12 North.
A pheresis machine, Hendrickson the RSL, Audrey King, and of course, the lab.
As I mentioned, and I should point out, that as I said, we're trying to get an Ind right now for long till. And that's based on funding we got from the office floor, and I think I'll leave it at that.
Thanks everybody.
My great presentation. Really excellent. Let's see if there any questions from the audience chat room here. So this is from God.
00:23:56.120 --> 00:23:57.940 Looks like you’re so excited.

00:23:57.940 --> 00:24:00.040 Talk research on adding tablets and

00:24:00.040 --> 00:24:02.532 margin molecules or modules in T cells

00:24:02.532 --> 00:24:04.252 to get around challenging metabolic

00:24:04.252 --> 00:24:05.950 environment for exhaustion times.

00:24:05.950 --> 00:24:09.220 So there are there have been, you know, a

00:24:09.220 --> 00:24:12.226 lot of they’re going to have a bunch of

00:24:12.226 --> 00:24:15.045 studies in mice that are really fantastic.

00:24:15.050 --> 00:24:17.228 Actually, some of the best ones.

00:24:17.230 --> 00:24:19.420 I think we’re from Sue Keck,

00:24:19.420 --> 00:24:22.692 used to have a cancer biology lab cancer

00:24:22.692 --> 00:24:25.286 Menology lab here and now she’s at.

00:24:25.290 --> 00:24:28.311 Assault or or scripts.

00:24:28.311 --> 00:24:29.339 I don’t know which,

00:24:29.340 --> 00:24:32.208 but she’s in California, but absolutely.
So there’s no question that in mice you can knock down metabolic pathways, making T cells much more tolerant of the toxic micro environment in the tumor. Now that hasn’t yet been done in people. People have been doing screens to look at to make T cells more effective, and either party or till, and so there might be a company out there that has done that, or we just don’t know. But absolutely, that’s a huge area of research.
by a lot of people, and I think we will definitely at some point the future be seen. Carty cells that have metabolic pathways altered based on this.

This is some recent data looking Dyson kinase and using that as a way of overcoming, I’ll.

There being no troubles me design right now. There being no troubles me design right now.

Look at this picture.

Next comment is from Marcus Poison Bird.

Nice presentation, just to mention.

Let’s try this myself.

Every efforts include developing
Massapequa tillmanns.

Yes, absolutely.

I need to talk to you.

And Marcus, yes, very excited about that.

Ask questions.

Have party studies been performed patients in multiple Kartik loans simultaneously against multiple different energies?

How many tourists again, is it generally available?

Is detention targets in different types of solid tumors?

So I don’t know the answer to that,
but I can tell you what I do now.

So I think the idea of using multiple parties at once.

I think there’s a worry that when you do that and I think their data for this that multiple ones within a cell result in a decrement of the actual response that you need to have.

A lot of the same.

You need to have sort of.

The same cars activate it all at once to really get a good response.

We have too many androgens.

It doesn’t, I think, work as well like you basically.
dilute out the response.

That's what I think.

He basically diluted out.

Now there are there have been people who are designing right now parties that are.

Their heritage, their heterodimers, so one of the antibody chains is to one target.

One of the antibody chains to another target that's only going to work if you have really high levels of both antigens.

Obviously on the cell, but those are inexperienced or those are being experimented on right now and we'll see how those work.
There's a real question about if you do that, you're not going to get the binding is not going to be as good regarding the number of tumor specific antigens. Again, it probably varies from cell to cell. That the older studies seem to indicate that these are very old studies, so it's very hard to know what that means. But for the till studies in some of the patients, when I looked at the ones who had really good responses. It did look as though. It was usually one dominant clone. Sometimes there were two dominant clones.
It’s hard to know exactly what those data were, as was a very limited number of patients, and it’s hard to know that they were looking at the right time. Like maybe the clone was there did a lot of what it’s supposed to do, and then a lot of it disappeared from the blood for some reason, so it’s very hard to know how much that’s real. The last thing I would say, though, is that it looks as though the most important antigens are private neoantigens, meaning they’re not these big targets that we do, and that’s really a worry.
NOTE Confidence: 0.8840049
00:28:15.090 --> 00:28:16.750 for car T cells in general,
NOTE Confidence: 0.8840049
00:28:16.750 --> 00:28:17.575 for solid tumors.
NOTE Confidence: 0.8840049
00:28:17.575 --> 00:28:19.920 So that is sort of a separate issue.
NOTE Confidence: 0.6741931
00:28:21.880 --> 00:28:24.100 Terrific Mike is always great presentation,
NOTE Confidence: 0.6741931
00:28:24.100 --> 00:28:27.430 so like to move on to our second speaker,
NOTE Confidence: 0.6741931
00:28:27.430 --> 00:28:29.280 Doctor IRA, Sufi doctor Susan,
NOTE Confidence: 0.6741931
00:28:29.280 --> 00:28:30.390 System Professor of
NOTE Confidence: 0.6741931
00:28:30.390 --> 00:28:31.870 Medicine and Hematology Co.
NOTE Confidence: 0.6741931
00:28:31.870 --> 00:28:34.090 Directed the adult Carty salty program.
NOTE Confidence: 0.6741931
00:28:34.090 --> 00:28:35.770 She received her medical emergency
NOTE Confidence: 0.6741931
00:28:35.770 --> 00:28:38.299 nurse in New York at Stony Brook
NOTE Confidence: 0.6741931
00:28:38.299 --> 00:28:40.645 and completed a fellowship at Yale
NOTE Confidence: 0.6741931
00:28:40.645 --> 00:28:42.230 University School of Medicine.
NOTE Confidence: 0.6741931
00:28:42.230 --> 00:28:44.827 Doctor seems clever work is in the
NOTE Confidence: 0.6741931
00:28:44.827 --> 00:28:46.669 area of hematological in season.
NOTE Confidence: 0.6741931

56
Tallest algic stem cell transplantation for his commissions as part of New Sweden legacy programming transplant teams. She developed a strong interest in the president, promised she’s focused her efforts in treating patients with aggressive, more focus as part of clinical trials solid in the response to treatment without August or outdated. Translate based on the specifics of specific seeds. As to director of the car T cell therapy product Spell Cancer hospital doctor Soupy. As part of a team that brings interview Milliman therapy treatments
00:29:17.623 --> 00:29:19.373 options to patients with certain
types of blood cancers doctors.

00:29:19.373 --> 00:29:21.250 Thank you very much for having me.

00:29:36.100 --> 00:29:37.360 Can you see my slides?

00:29:39.860 --> 00:29:44.660 Now you know. Well, you know I have.

00:30:15.820 --> 00:30:16.290 Yeah.

00:30:19.060 --> 00:30:19.999 Yep, that’s great.

00:30:22.050 --> 00:30:24.654 Thank you so my focus today is
going to be in South therapist

00:30:24.654 --> 00:30:27.358 and what we’re doing here at Yale.

00:30:34.908 I have a couple of bad disclosures.
So the I'd like to update you today on some of the FDA approved indications for cell therapies and he malignancies, which are growing by the day. Some of our research strategies to improve response rates and prevent resistance to cell therapies. Some of the challenges we're facing clinically and research wise. And then I'd like to end the presentation by giving you an idea about the work that we're doing here at DL as part of our immune cell therapy dart for hematologic malignancies and then some of the Inter institutional research collaborations that we
have started to work on.

So, as Mike mentioned, there’s been an evolution in chimeric antigen receptors.

Overtime, the once we are still using in the clinic that are commercially approved, our second generation cars, but there is some innovative card design going on including suicide cars as a control mechanism for better toxicity management. This dual targeting cars that express.

Two different antigen specific cars by specifics where you have.
Add two linked SF Sfes within one core vector and then these TCR mimic cars that are important to address HLA presented antigen swear. You’re directing the CFP domain against a peptide HLA complex. Initially the the target was CD 19 for B cell malignancies because as you all know it’s a pan bissan marker, its expression is generally restricted to B cells and their precursors and represent it’s it’s surface molecules, so it’s represented irrational target for therapy and he malignancies and so all of the agents that are approved for commercial use.
Or directed at city 19. So we started initially back in 2019. The first approval with that DISA, gentle occlusal in pediatric LL and subsequent to that we’ve had a series of approvals including this agenda, Cluzel and Axicabtagene Silo Loosle for aggressive diffuse large B cell lymphoma, transformed follicular lymphoma and then. Lisso catagen merilou. So where you are giving the cells differently because it’s a defined CD4 to CD8 ratio, so there is some novelty compared to the two previously approved products and then more recently Brexit.
catagen auto loosle just in the last year for mantle cell lymphoma. Anan, finally, you know just a few weeks ago Axicabtagene Silo Loosle for relapsed refractory follicular lymphoma. So the response rates that we see with these drugs, particularly in low grade lymphomas like follicular, are extremely good with very high overall response rate and complete response rates in pretreated patients, and then in diffuse large B cell lymphoma and aggressive deal BCL or transformed the complete response.
rates have varied anywhere from 30 to 50% even though the initial overall response rates. Are very high, so these are still very good outcomes. Don’t get me wrong for this group of patients, you know the predicted long term. Survival is typically less than 10% when they go on to get CAR T cell therapies. So we’ve really been able to to cure a good subset of those patients. But as you can see, you know we still have a long way to go in aggressive lymphomas be cause.
Even of the patients were cheap

Complete remission only about 2/3 are able to maintain that, but it's very.

It’s very exciting because just in the last couple of years we now have all of these products that are commercially approved for use and that we are already using here at Yale.

So the other rational target was BCM may in multiple myeloma, which is highly expressed on malignant plasma cells.

And we know that higher concentrations of soluble BCM mayor also associated with poor outcomes in multiple myeloma.
This is very essential in regulating B cell maturation and differentiation. And so there have been a series of phase one and two studies looking at PCM. A directed car T cells. And particularly the first one I did, captain be cluzel, is actually very close to approval. These were very heavily pretreated patients with a median number of treatments being about 6. And as you can see, the overall response rates are extremely good and even complete response rates. I’m.
Are are very good and so.

There is of course toxicity like we saw with anti CD 19, particularly cytokinin release and neurologic toxicity, but again this is a very difficult population of patients to treat. The majority of them were what we call triple refractory to emits an proteasome inhibitors and about 25% of patients were pent. These are extremely good outcomes for this. For this patient population. And there’s now a race to get FDA approval in the USA.
Not just only for I decapped agenda cluzel but but also for. For several other products and there are efforts being made to introduce them earlier in earlier phases of disease and comparing them to the standard of care which is autologous stem cell transplant. And then there are already efforts being made to mitigate antigen escape by combining. For example, PC MA Carty with CD19 CAR targeting other other antigens. So the same cannot be said for acute myeloid leukemia, unfortunately, which has been, you know,
a great challenge over the years.

And because many of the potential target antigens are actually intracellular,

their tumor associated antigens or NEO antigens and.

And the proteins that are expressed on the surface of the malignant leukemic cells, like City 33,

you know some of those markers are also expressed on.

Hammer away **** stem cells and so.

The trials going on have had to consolidate.

Cortisol therapy or rescue I should say the the mirror with an allogeneic stem cell transplant.

So there are several critical
and resolved issues with car T cell therapy in malignancies, and I would categorize them in failure to achieve remission, disease, relapse, toxicities with car T cell and then some of the toxicity. Some of the challenges in moving beyond Bissell LL and diffuse large B cell lymphoma, two other diseases that may not necessarily. Have high expression of surface markers. Easy to visit that are easy to target with cortisol therapy or certain diseases where. Malignant clone, residing inside a lymph
NOTE Confidence: 0.77998555

00:39:43.050 --> 00:39:46.169 node and not necessarily in the circulation.

NOTE Confidence: 0.77998555

00:39:46.170 --> 00:39:49.466 Like with Abyssal LL and so there’s that

NOTE Confidence: 0.77998555

00:39:49.466 --> 00:39:52.012 challenge of the tumor microenvironment

NOTE Confidence: 0.77998555

00:39:52.012 --> 00:39:55.827 prohibiting the T cells from getting there.

NOTE Confidence: 0.77998555

00:39:55.830 --> 00:40:00.226 So. What is it that?

NOTE Confidence: 0.77998555

00:40:00.226 --> 00:40:03.040 Predicts outcome from a patient perspective.

NOTE Confidence: 0.77998555

00:40:03.040 --> 00:40:06.768 Ann and risk factors that we can outline

NOTE Confidence: 0.77998555

00:40:06.768 --> 00:40:10.208 before they go onto car T cell therapy.

NOTE Confidence: 0.77998555

00:40:10.210 --> 00:40:12.912 So there was this large study that

NOTE Confidence: 0.77998555

00:40:12.912 --> 00:40:15.726 looked at baseline factors that were

NOTE Confidence: 0.77998555

00:40:15.726 --> 00:40:18.351 associated with worse overall survival

NOTE Confidence: 0.77998555

00:40:18.351 --> 00:40:20.717 and progression free survival in

NOTE Confidence: 0.77998555

00:40:20.717 --> 00:40:23.195 patients who got standard of care.

NOTE Confidence: 0.77998555

00:40:23.200 --> 00:40:23.647 Axicabtagene,

NOTE Confidence: 0.77998555

00:40:23.647 --> 00:40:27.223 Sila Loosle and as you can see here,

NOTE Confidence: 0.77998555

00:40:27.230 --> 00:40:30.032 there were several factors that were
statistically significantly associated.

With worse outcomes and in particular.

I would outline here patients that had high bulk of disease and patients that had, for example,

elevated LDH levels pre transplant patients who required bridging therapy also were at higher risk of having worse overall survival and progression free survival, perhaps because both of these things are a surrogate for a higher disease burden, and then Interestingly some of the other factors that were associated with outcomes. Were younger age and also
male gender and that is. Very different from what we see. Included in our prognostic indices for lymphomas where actually older patients tend to do worse, and this means that we need to really, really look at our prognostic markers in the era of cell therapy and really redefine what relevant clinical risk factors are. So this is showing a multivariable model of Afexa cottage inside a looser treated patients, where again having. Poor performance status and also having high elevated,
NOTE Confidence: 0.77998555
00:42:01.190 --> 00:42:03.740 high LDH levels is associated
NOTE Confidence: 0.77998555
00:42:03.740 --> 00:42:05.270 with worse progression,
NOTE Confidence: 0.77998555
00:42:05.270 --> 00:42:09.240 free survival and overall survival.
NOTE Confidence: 0.77998555
00:42:09.240 --> 00:42:12.030 And then what about, you know,
NOTE Confidence: 0.77998555
00:42:12.030 --> 00:42:14.350 the the the disease itself?
NOTE Confidence: 0.77998555
00:42:14.350 --> 00:42:18.214 One of the things that we already know
NOTE Confidence: 0.77998555
00:42:18.214 --> 00:42:22.214 is that about 25 to 30% of patients
NOTE Confidence: 0.77998555
NOTE Confidence: 0.77998555
00:42:26.960 --> 00:42:30.272 Experienced loss of CD 19 and
NOTE Confidence: 0.77998555
00:42:30.272 --> 00:42:31.928 this was demonstrated.
NOTE Confidence: 0.77998555
00:42:31.930 --> 00:42:34.540 Inazuma 1 trial and the US
NOTE Confidence: 0.77998555
00:42:34.540 --> 00:42:35.845 Carty Lymphoma consortium.
NOTE Confidence: 0.77998555
00:42:35.850 --> 00:42:38.909 So it’s not the majority of patients,
NOTE Confidence: 0.77998555
00:42:38.910 --> 00:42:40.275 particularly in lymphoma,
NOTE Confidence: 0.77998555
00:42:40.275 --> 00:42:45.009 but it is a good subset and so you know what.
NOTE Confidence: 0.77998555

74
What can we do?

To prevent antigen loss and then also this PD One PDL,

Because we know that PDL one up regulation is actually contributing to CART exhaustion so.

We have this publication nice publication in Nature Medicine from 2020,

Nirav Shah at Wisconsin, actually looked at point of care manufactured by specific anti CD 20 and anti CD 19 CAR T cells in relapsed malignancies.

In some of these patients had already undergone anti CD 19 CAR T cell therapy.
And they do see ongoing responses in about 40% of patients, I think out of about 60% that responded initially and they did not observe loss of CD 19 in progressing patients when they. So really very very exciting data. And then just this year. They presented results of a first CD targeting Bicistronic with humanized binders, to reduce image unicity, to reduce image unicity, and in addition to 41 BB costimulatory.
they also edit OX 40 to improve persistence. So based on that?

Data they went on to do a single arm open label multicenter phase. One two study where they did tool dual targeting of CD 19 and CD 22. But they also added Pember Lizum app for relapsed refractory diffuse large B cell lymphoma and Interestingly. What they saw is there is a high rate of complete response is about 66%, although it’s too early to say you know how. If they’re going to be durable and how durable they will be, because right now they. They only have short term a data,
but Interestingly there was very little toxicity with this particular construct. They did not see any grade three or four cytokine release or neurologic toxicity. And that perhaps really is a reflection of this. Really novel novel technology that they’re using with a novel pentameric spacer, and this humanized binders so this data is very exciting because it’s a therapy that we might be able to use if approved eventually in the outpatient setting and delivered in the outpatient setting. And that’s where they’re really
going with this. So I'm.

What else do we know about the?

The disease aspect itself that may make response to cortisol therapy.

Challenging, so this data from the Juliet study,

They looked at the Myc expression and tumor infiltrating T cells in that study,

and what they actually found was that baseline mic negative status was actually associated with significantly improved outcome compared to Nick positive patients.
And that included also longer median duration of response and overall survival. And when they looked at the tumor microenvironment analysis of the baseline biopsies, what they saw is that lack or low frequency of tumor infiltrating CD3 positive T cells was also associated with short progression free survival compared to patients that had more than 3% CD3 T cells. In the tumor so taken together, these results suggest that make overexpression or an unfavorable immunosuppressive tumor microenvironment
00:47:25.519 --> 00:47:28.285 with a restricted T cell response
NOTE Confidence: 0.47944975
00:47:28.285 --> 00:47:30.520 may impact score efficacy in
NOTE Confidence: 0.47944975
00:47:30.520 --> 00:47:32.998 patients with large B cell lymphoma.
NOTE Confidence: 0.8249064
00:47:37.860 --> 00:47:40.795 And then this publication and
NOTE Confidence: 0.8249064
00:47:40.795 --> 00:47:43.730 Oncotarget looked at mutations or
NOTE Confidence: 0.8249064
00:47:43.831 --> 00:47:47.184 copy number losses of CD58 and TP53.
NOTE Confidence: 0.8249064
00:47:47.190 --> 00:47:50.368 Genes in diffuse large B cell lymphoma
NOTE Confidence: 0.8249064
00:47:50.368 --> 00:47:53.837 and showed that these are independent
NOTE Confidence: 0.8249064
00:47:53.837 --> 00:47:56.529 unfavorable prognostic markers so.
NOTE Confidence: 0.891362
00:47:58.900 --> 00:48:04.588 What we know about City 58 is that.
NOTE Confidence: 0.891362
00:48:04.590 --> 00:48:08.027 This is actually binds CD two and
NOTE Confidence: 0.891362
00:48:08.027 --> 00:48:12.137 the T cells and T cell mediated
NOTE Confidence: 0.891362
00:48:12.137 --> 00:48:15.929 cytotoxicity and also NK cell mediated
NOTE Confidence: 0.891362
00:48:16.047 --> 00:48:20.517 cytotoxicity is actually quite important.
NOTE Confidence: 0.891362
00:48:20.520 --> 00:48:23.180 And quite dependent on the
NOTE Confidence: 0.891362
On the tumor tissue.

So in Ash 2020 they presented data looking at 58 mutations and circulating tumor DNA is tumor DNA and they showed that this was associated with poor outcome. After Axicabtagene sila loosle.

These 358 mutations are or loss are common and they occur in about 20% of patients with diffuse large B cell lymphoma and then in addition to that the protein City 58 protein expression is also directly related somewhere between 60 to 80% to 70% of patients with diffuse large B cell lymphoma.
His do regulate have deregulation of the CD 58 protein expression.

And as you can see here, they were able to show that loss of this expression was also associated with worst outcomes were in blue.

Fewer patients that had loss of CD 58 expression actually went on to achieve complete remission. The majority either did not respond or they achieved only partial remission. And then they went on to to progress.

So, meisner. Amazing group.
Presented this data very, very interesting this year at ASH where they showed that integrating City 22 costimulation within cells was actually able to overcome City 58 loss in tumor cells and they tried this both insists an entrance and it wasn’t until they integrated it entrance that they saw that they saw these. These results so. This was very eye opening for us because, we used to think that. All of the costimulation is coming from other cells. And we didn’t really realize how.
important actually ceded to City to
was in in in car mediated cytotoxicity.
So City 5862 was a very novel
axis of car resistance that was uncovered through deep correlative
studies in patients getting cell therapies and city 58 loss,
or mutation pretends a poor outcome, but perhaps we can overcome that by engineering these cars that integrates it is 2 signaling in entrance and it is 2 signaling in entrance and this is important because City 58
Lawson mutations are also common in. Other cancers in are likely able to mediate resistance to other cars and immunotherapeutics,
so it could perhaps be applied in other malignancies outside of diffuse large B cell lymphoma.

So I’ve spoken to you about the relapse reflect setting, but we are now doing studies pushing these cellular therapies in the second line, and even in the first line settings, Uma 12 looked at very high risk patients with high grade B cell lymphoma. With Myc, BCL, two and BCL 6 translocations, and they did pet directed therapy and for patients who still had disease after two cycles by PET scan.
They actually went on to get their T cells collected and then receive Car T cell therapy. So these are the results. They saw a very high 85% of the overall response rate with 74% CRS. This is a difficult group of patients for us to treat because oftentimes they do not achieve remission and they progress right through therapy. The car T cell expansion was greater in this study when compared to Zuma one which were.

Patients with relapsed refractory disease were treated so so higher quality T cells with higher,
with higher proliferation and higher expansion. So this has not.
Obviously it’s not prime time for us to change our decision-making and move this to to first line therapy, but there is definitely improved T cell fitness in first line treatment and this may be the wave of the future when we get more long term data. So just to sort of recap for you, some of the studies in relapsed refractory disease and. Also to include some data with CLL and mantle cell lymphoma,
as you can see very high overall response rates across the board and then somewhere between 50 and 75% complete remission rates in relapse patients. So where are we going with this? As I mentioned, we’re trying to introduce them earlier in the lines of therapies. So many phase three studies looking at second line for transplant eligible patients, randomizing them to transplant versus Carty and then and then perhaps eventually in the front line and then in a LL patients looking at patients one or MRD positive after one line of therapy.
And then hopefully some of these phase three data in adults will result in an approval because we still don’t have an approval in a LL for patients over the age of 25. So what about alginate cars is, as you know, there are some limitations with autologous CAR T cells, particularly in terms of cost harvesting and manufacturing failures and disease really progressing during manufacture, and we can really bypass a lot of that with donor derived. Sales where we can really reduce the time to infusion significantly and actually
be able to take more patients to Carty. And there's an increased probability of healthy cortisol generation and the convenient of repeat dosing if necessary. So these are some of the investigational allogeneic CAR T cells for him malignancies. Targeting different antigens both in lymphomas AALL, but also in multiple myeloma. This is still early phase one phase two data, but I think that this is going to be the wave of the future in Carty, so I'm going to now shift gears to just briefly talk about our cortisol therapy program here at heel we started our efforts in 2018 and were.
Able to eventually treat our first patients in January of 2019 and then were able to actually achieve fact accreditation after extensive auditing of our program.

So this is our organizational chart. As you can see, it includes collaboration between multiple departments. Physicians nursing program self therapy with Diane and Alexianne. We have a really trained group of people being able to freeze the patients and...
then and then give the conditioning therapy and manage the toxicities. So what have we done in the last two years with 357 patients, some of them with axicabtagene, sidlu, We're just starting to actually expand to mantle cell lymphoma and then follicular lymphoma. And we've also treated 11 patients on clinical trial for multiple myeloma with anti BCMAM RNA CAR T cells. And as Mike mentioned there are some there is much less toxicity. But there are also challenges in terms of. In terms of the short life of the M RNA,
and perhaps the need for frequent dosing or maybe introducing this in earlier lines of therapy where patients do not have a very heavily pretreated and do not have an extensive burden of disease with a new approval and multiple myeloma expected this year, there's actually an anticipated significant rise in numbers of patients that were going to be treated. And what that means is that we can collect a lot more data and do a lot of studies on patient samples. So this is the yellow advanced cell.
therapy lab and then this is our immune effector cell therapy dart that Mike and I call lead and and we have a team as he spoke about. I won’t belabor this, but we wouldn’t be able to do what we do without their amazing work. So this is our portfolio. We have some studies that were opened and finished accrual, but as you can see we have a large number of. Pending studies at the majority of which are very novel because they are either by specific cars or their allogenic cars sitting 19 NK cars and. You know, really also these comparative...
randomized comparative studies introducing car T cells in the earlier lines of therapy. You know, we really took a set back with Chobit, but we really hope to be able to open all of these studies in the next few months and start enrolling patients. So this is. These are some of our instruct intra institutional research collaborations with Doctor Mina Xuan, Doctor Jordan Pober in Pathology, looking at the vasculature in the human lymphoma nodal micro environment collaboration with shall issue. Looking at these phase cars for low antigen expressing B cell cancers and
00:59:30.244 --> 00:59:32.909 then collaborations with City Chen.

NOTE Confidence: 0.84343517

00:59:32.910 --> 00:59:35.898 So in the interest of time,

NOTE Confidence: 0.84343517

00:59:35.900 --> 00:59:38.188 I will just briefly.

NOTE Confidence: 0.84343517

00:59:38.188 --> 00:59:40.887 Discuss these collaborations, but.

NOTE Confidence: 0.84343517

00:59:40.887 --> 00:59:43.818 As you know.

NOTE Confidence: 0.84343517

00:59:43.820 --> 00:59:47.260 Getting the T cells to the tumor tissue

NOTE Confidence: 0.84343517

00:59:47.260 --> 00:59:49.658 and increasing homing is actually

NOTE Confidence: 0.84343517

00:59:49.658 --> 00:59:52.574 quite a challenge for most patients,

NOTE Confidence: 0.84343517

00:59:52.580 --> 00:59:55.442 and there have been several attempts

NOTE Confidence: 0.84343517

00:59:55.442 --> 00:59:58.443 overtime looking at how we can

NOTE Confidence: 0.84343517

00:59:58.443 --> 01:00:00.459 improve homing for lymphocytes.

NOTE Confidence: 0.84343517

01:00:00.460 --> 01:00:02.280 Including cell surface painting,

NOTE Confidence: 0.84343517

01:00:02.280 --> 01:00:03.190 for example,

NOTE Confidence: 0.84343517

01:00:03.190 --> 01:00:05.006 to insert alphabeta integrin

NOTE Confidence: 0.84343517

01:00:05.006 --> 01:00:06.368 into primary lymphocytes,

NOTE Confidence: 0.84343517

01:00:06.370 --> 01:00:09.100 including glyco engineering CAR T cells,
for example, to enforce E selectin binding because as many of you may know, car T cells do not express sialyl Lewis X and do not bind deselecting, but we can actually achieve enforce their display on human CAR T cells by surface fucosylation and this will. Results in very robust E selectin binding even under conditions of hemodynamic shear and then also gene therapy using genetically modified lymphocytes targeting VEGF or two in highly vascularized tumors. But unfortunately all of this data is
in mice and we don’t really know what’s happening in the human tumor vessels, and we do not have any idea about the spatial relations of these two of these tumor infiltrating lymphocytes, so the aim of our study is to employ highly multiplexed immunofluorescent imaging of human lymphomas to specially correlate and phenotype. The infiltrating even of sites using formalin fixed and. Not been embedded tissue specimens, and then we want to apply these results to investigate the informer vasculature in car T patients. Pretreatment and posttreatment.
This is Nathan Paulsen, one of the residents in pathology, and he’s already looked at some. Or lymphoma tissue samples showing that there are differences in expression levels of vascular adhesion molecules. For example, between diffuse large B cell lymphoma, classical Hodgkin lymphoma and T cell rich, large B cell lymphoma. And so we want to do high dimensional phenotyping of these vascular cell samples in FPED identified tumor samples looking and all of these, all of these vascular markers and
the we anticipate to find some correlation of the vessel phenotypes with the abundance and phenotype of the leukocytic infiltrates and to correlate there this with the patients outcomes post car T cell therapy. If we're lucky, we're going to be able to show that some two rationale for combining these CAR T cell therapies with antiangiogenic therapies, particularly. And this can be a launching point for us to actually eventually in the future consider a trial.
So this is some of the data from Chalet Sues Lab where he’s using these face cars where targeting specifically low density surface antigen and he’s been able to show that car signaling is different from T cell receptor signaling and that it bypasses certain proteins like latch. And has a different pathway that results in acting polar MIS polymerization compared to TCR signaling, and he’s actually using this information to develop these phase cars on lipid bilayers that he can modulate to recognize low density surface antigens.
So this is again some of the data that he is generated in his lab where he’s been able to show that Corti signaling bypasses this important scaffold. He’s been able to build this face where they contain and you control modality that can leverage domains affecting phase separation to modulate Carty activity recognizing low density surface antigens. He’s constructed Roger B cells expressing low to High City 19 and this is just some very preliminary data that he has showing that this point phase cars display superior
01:04:23.961 --> 01:04:26.416 activity compared to control parties.

01:04:26.420 --> 01:04:26.881 Again,

01:04:26.881 --> 01:04:30.569 low against low CD 19 so we are

01:04:30.569 --> 01:04:34.651 hoping to look now at some of our

01:04:34.651 --> 01:04:37.289 patients blood samples that have.

01:04:37.290 --> 01:04:40.350 Low CD19 expressing he malignancy’s

01:04:40.350 --> 01:04:43.410 either at baseline or following

01:04:43.509 --> 01:04:46.708 treatment with CD19 CAR T cell therapy

01:04:46.708 --> 01:04:49.853 and and and showing how these pace

01:04:49.853 --> 01:04:53.384 cars will be able to to act against

01:04:53.384 --> 01:04:55.894 these low CD19 expressing tumors.

01:04:55.900 --> 01:04:59.092 And then we’re also hoping the

01:04:59.092 --> 01:05:01.811 future to collaborate with City

01:05:01.811 --> 01:05:04.781 Chen looking at these dual knock

01:05:04.781 --> 01:05:08.039 in knockout CAR T cells that he’s.

01:05:08.039 --> 01:05:10.219 And then we’re also hoping the
Engineered in his lab targeting two different antigens on lymphoma cells and and.

Doing PT one knockout.

So this is our group and.

This is our group of people and I'm very thankful for their work and I went a little over time so I'm happy to answer any questions.

So I don't think there's any questions on the Chatroom at this point so.

I was thank you for a terrific presentation.

Thank you, thank you.